TRPV4 gene

transient receptor potential cation channel subfamily V member 4

Normal Function

The *TRPV4* gene provides instructions for making a protein that acts as a calcium channel. This channel, which transports positively charged atoms of calcium (calcium ions) across cell membranes, is found in many types of cells and tissues. Studies suggest that the TRPV4 channel plays a role in a number of different functions in the body. These include the development of bones and cartilage, the tough but flexible tissue that makes up much of the skeleton during early development. It is also be involved in maintaining the body's water balance (osmoregulation) and in certain types of sensation, particularly the sensation of pain. The TRPV4 channel may also play a role in the self-destruction of cells (apoptosis). It likely has additional functions that have not been identified.

Health Conditions Related to Genetic Changes

Charcot-Marie-Tooth disease

At least seven mutations in the *TRPV4* gene have been found to cause Charcot-Marie-Tooth disease type 2C (also called hereditary motor and sensory neuropathy type 2C). This condition affects the peripheral nerves, which connect the brain and spinal cord to muscles and to sensory cells that detect sensations such as touch, pain, heat, and sound. Charcot-Marie-Tooth disease causes loss of sensation, muscle weakness and wasting (atrophy) of muscles in the feet, hands, and legs. Charcot-Marie-Tooth disease type 2C caused by *TRPV4* gene mutations has additional signs and symptoms that do not usually occur in other forms of the disorder. These additional signs and symptoms include hearing loss caused by nerve damage in the inner ear (sensorineural hearing loss), vocal cord weakness resulting in a hoarse voice, and weakness of the muscle that separates the abdomen from the chest cavity (the diaphragm), which can cause breathing problems.

The *TRPV4* gene mutations responsible for Charcot-Marie-Tooth disease type 2C each change a single protein building block (amino acid) in the TRPV4 calcium channel. Studies suggest that these mutations overactivate the channel, increasing the amount of calcium that can flow into cells. It is unclear why this change specifically affects the nervous system and how the change is related to the particular neurological problems associated with this condition.

metatropic dysplasia

At least 10 mutations in the *TRPV4* gene have been identified in people with metatropic dysplasia, a skeletal disorder characterized by short stature (dwarfism) with other skeletal abnormalities. Most of these mutations change single amino acids in the TRPV4 calcium channel. However, a few mutations insert or delete pieces of DNA in the *TRPV4* gene.

Studies suggest that the *TRPV4* gene mutations that cause metatropic dysplasia overactivate the TRPV4 calcium channel. The resulting increase in calcium in cartilage-forming cells (chondrocytes) may disrupt the early development of cartilage and bone. However, it remains unclear why these mutations affect chondrocytes specifically and how changes in TRPV4 channel activity result in the particular skeletal abnormalities associated with metatropic dysplasia.

other disorders

Mutations in the *TRPV4* gene cause a variety of other conditions, most of which affect the developing skeleton or the nervous system.

In addition to metatropic dysplasia, skeletal disorders associated with *TRPV4* gene mutations include autosomal dominant brachyolmia; spondylometaphyseal dysplasia, Kozlowski type; spondyloepiphyseal dysplasia, Maroteaux type; and parastremmatic dysplasia. These related conditions involve combinations of short stature, abnormal side-to-side and back-to-front curvature of the spine (kyphoscoliosis), and other problems with developing bones.

Mutations in the *TRPV4* gene also cause neurological disorders. In addition to Charcot-Marie-Tooth disease type 2C, this spectrum of related conditions includes congenital distal spinal muscular atrophy, which is characterized by weakness of muscles in the legs and hips, and scapuloperoneal spinal muscular atrophy, which involves weakness and wasting (atrophy) of muscles in the shoulders and lower legs.

Most of the *TRPV4* gene mutations that cause these skeletal and neurological disorders change single amino acids in the TRPV4 calcium channel. These mutations likely result in an overactive channel, although some research suggests that the mutations may have different effects on channel function in different tissues. Certain *TRPV4* gene mutations have been found to cause skeletal disorders in some people and neurological disorders in others. Additionally, some *TRPV4* gene mutations can cause both skeletal and neurological features in the same individual. Researchers are working to determine how *TRPV4* gene mutations can cause this wide variety of signs and symptoms.

Another bone disorder, known as familial digital arthropathy-brachydactyly, has also been associated with mutations in the *TRPV4* gene. This condition is characterized by arthritis in the joints of the fingers and toes (arthropathy) and shortened fingers and toes (brachydactyly). The mutations that cause this condition appear to impair

the function of the TRPV4 calcium channel, preventing it from transporting calcium ions effectively. It is unclear how a loss of channel function leads to the specific features of this condition.

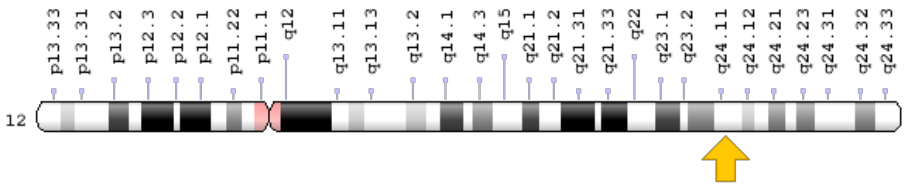
Common variations (polymorphisms) in the *TRPV4* gene have been associated with two additional disorders: hyponatremia, which is a condition of water imbalance that can cause dangerous brain swelling, and chronic obstructive pulmonary disease (COPD), a common lung disease that causes difficulty breathing. It has not yet been determined how differences in the function of the TRPV4 calcium channel are related to these two conditions.

Because mutations in the *TRPV4* gene are associated with such a wide array of conditions, some researchers have proposed referring to all *TRPV4*-related disorders as *TRPV4*-associated peripheral neuropathy and bony dysplasias (*TRPV4*-PNAB) or *TRPV4*-opathies.

Chromosomal Location

Cytogenetic Location: 12q24.11, which is the long (q) arm of chromosome 12 at position 24.11

Molecular Location: base pairs 109,783,087 to 109,833,407 on chromosome 12 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- osm-9-like TRP channel 4
- OSM9-like transient receptor potential channel 4
- osmosensitive transient receptor potential channel 4
- OTRPC4
- SPSMA
- SSQTL1
- transient receptor potential cation channel, subfamily V, member 4

- transient receptor potential protein 12
- TRP12
- TRPV4_HUMAN
- vanilloid receptor-like channel 2
- vanilloid receptor-related osmotically activated channel
- VR-OAC
- VRL-2
- VRL2
- VROAC

Additional Information & Resources

Educational Resources

- TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades (2007):TRPV4: A Multifunctional Nonselective Cation Channel with Complex Regulation
  https://www.ncbi.nlm.nih.gov/books/NBK5242/#ch9

GeneReviews

- Charcot-Marie-Tooth Neuropathy Type 2
  https://www.ncbi.nlm.nih.gov/books/NBK1285
- TRPV4-Associated Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK201366

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28TRPV4%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- BRACHYOLMIA TYPE 2
  http://omim.org/entry/613678
- BRACHYOLMIA TYPE 3
  http://omim.org/entry/113500
- DIGITAL ARTHROPATHY-BRACHYDACTYLY, FAMILIAL
  http://omim.org/entry/606835

- NEURONOPATHY, DISTAL HEREDITARY MOTOR, TYPE VIII
  http://omim.org/entry/600175
- PARASTREMMATIC DWARFISM
  http://omim.org/entry/168400
- PULMONARY DISEASE, CHRONIC OBSTRUCTIVE
  http://omim.org/entry/606963
- SCAPULOPERONEAL SPINAL MUSCULAR ATROPHY
  http://omim.org/entry/181405
- SPONDYLOEPIPHYSEAL DYSPLASIA, MAROTEAUX TYPE
  http://omim.org/entry/184095
- SPONDYLOMETAPHYSEAL DYSPLASIA, KOZLOWSKI TYPE
  http://omim.org/entry/184252
- TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY V, MEMBER 4
  http://omim.org/entry/605427

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_TRPV4.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=TRPV4%5Bgene%5D
- HGNC Gene Family: Ankyrin repeat domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/403
- HGNC Gene Family: Transient receptor potential cation channels
  http://www.genenames.org/cgi-bin/genefamilies/set/249
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=18083
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/59341
- UniProt
  http://www.uniprot.org/uniprot/Q9HBA0

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Reviewed: March 2013
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
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